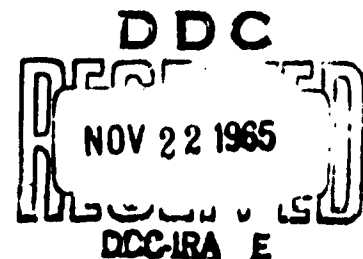
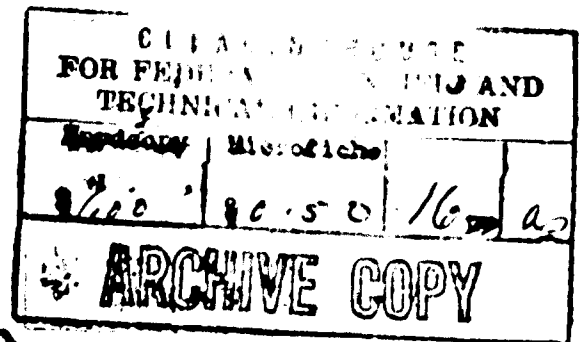
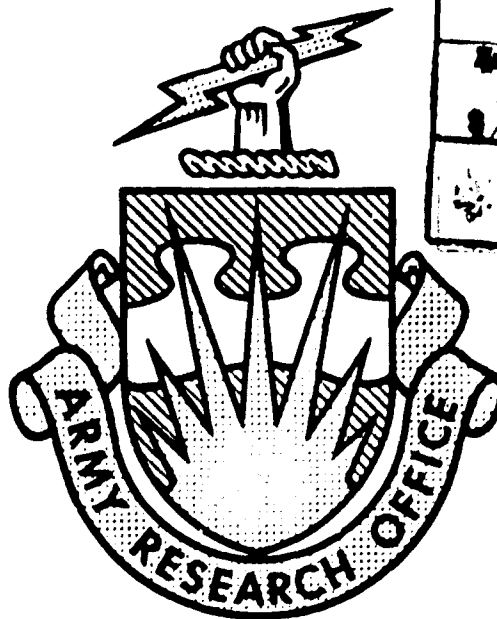


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Research Report

Effects of Psychopharmacologic Drugs Upon Sensory Inflow in Normal Subjects,
Psychiatric Patients and in Animals

FINAL REPORT

By: Dr. Elio Garcia Austt

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URUGUAY

Effects of Psychopharmacologic Drugs Upon Sensory Inflow in Normal Subjects, in Psychiatric Patients and in Animals

Final Technical Report

Grant Nº DA-ARO-49-002-64-G40

Defense Research Office (U. S. Army)

ELIO GARCIA AUSTT

principal investigator

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1. INTRODUCTION

The present technical report is concerned with the investigation carried out from October 1, 1964 to September 30, 1965 under Grant N° DA-ARO-49-092-64-G40.

The work was conducted by E. García Austt, M.D., Associate Professor of Physiology, Head of the Laboratory of Neurophysiology (Principal Investigator), J.I. Villar (Pharmacologist), O. Bachini, M.D. (Psychiatrist), J. Bogacz, M.D. (Neurophysiologist), S. Prieto (Neurophysiologist), M.D. Bottinelli, M.D. (Neurologist) and P. Handler (Medical Electronist).

The research was performed in the Laboratory of Neurophysiology of the Institute of Neurology, School of Medicine, Montevideo, Director Ramón Arana Iniguez, M.D., Professor of Neurology.

As stated previously, the specific aims of the research plan are as follows: (1) to establish what changes are observed in the sensory evoked potential in normal subjects by effect of barbiturates, lysergic acid and some other psychotropic drugs. These changes will be studied in different attentional levels and during habituation and conditioning. (2) To determine the same changes evoked by the same drugs in psychotic patients, especially in schizophrenics. (3) The effect of the same drugs on attention, habituation and conditioning will be studied in rats, guinea pigs and cats.

In the first year only the study of the first two aspects was started, a further one being added, the study of sensory information in comatose and stuporous patients.

To study the sensory evoked potentials techniques of averaging are necessary. Concomitantly with the clinical and physiological study some technical improvements were developed.

2. TECHNICAL DEVELOPMENT

This research was carried out by Handler.

For the detection of evoked potentials, the use of the magnetic tape method developed in this laboratory was continued. Later, a CAT computer was put to use but several drawbacks appeared in its application to the different experiments carried out in the laboratory. For this purpose, some minor modifications were made on the CAT, such as shortening of the readout and delay times. An original system was also devised that performs automatically the following sequence: accumulation during a preset time, reading out and simultaneous erasing, accumulation, etc. This system dispenses the CAT operator from carrying out the following operations: press the Start button, count the stimuli, press the Read Out button when the predetermined count is reached, wait for the end of the readout, press the Display button, press the Reset button, press the Start button, etc. A calibrating signal was also included in the system. This system was set up with minimal modifications in the apparatus, adding only a few resistors, one condenser and one diode.

This device will be reported in a publication which is in preparation.

3. CLINICAL AND PHYSIOLOGICAL RESEARCH

Experiments were conducted in three different directions. The first two correspond to the two first specific aims and the last one to the study of sensory information in the state of coma and stupor.

1. Effects of psychotropic drugs upon visual evoked response (VER) in normal subjects.

Aims of the work. The only drug studied so far was LSD 25. Because this substance provokes striking changes in perception it was thought of interest to determine whether there exist objective changes in the visual sensory inflow.

Method of procedure. Thirty-four experiments were carried out in 18 subjects. Continuous flicker stimulation with medium intensity flashes at a regular frequency of 0.67-1 per second was employed during 50 minutes. The subjects were placed in a dark room in a quiet environment. In most of the cases the study was performed in normal conditions and after the oral or intramuscular administration of 0.1 mg of LSD 25.

Results. The VER showed two important changes : (1) multiplication of the waves, particularly of the first components ; and (2) an increase of the amplitude particularly of the last components. But the most striking change was that the amplitude response instead of diminishing during continuous flicker stimulation as was constantly observed in normal subjects, increased along the

50 minutes of stimulation.

This phenomenon is related with the incapacity of the individuals submitted to the action of this drug to block the unnecessary or irrelevant information.

2. Characteristics of the visual evoked response in neurotic and psychotic patients and changes provoked by psychotropic drugs.

Aims of the work. In previous papers the characteristics of the averaged scalp visual evoked responses as well as the changes of the response as a function of time during sensory habituation in normal adults have been studied. In this work it is attempted to determine whether there exist any differences in the pattern of the response between normal and psychiatric subjects and whether the psychotropic drugs provoke in this latter group different changes in such a response.

Method of procedure. A hundred and four observations were performed in 74 patients with the same technique as described above.

To rule out the influence of repetition of sessions, patients are studied with repeated controls without the administration of drugs.

Obviously, this investigation poses numerous practical difficulties since we are concerned with patients submitted to treatment in whom the therapy usually involves several associated drugs which cannot be discontinued at will except in the case of strict medical indication.

Results. Despite the number of experiments carried out and owing to the

foregoing reasons, definitive results are still pending.

So far, the action of the following psychotropic drugs has been studied :

Chlorpromazine, Meprobamate, Dyazepan, Methedrine, Butyrophenone, Amphetamine, Fenzazine (Nardel or Nardelzine).

However, some previous results are stimulating. In some cases, particularly in the obsessive neurosis and hysteria, the normal reduction of VER amplitude observed during photic habituation was not found. Chlorpromazine reduced the amplitude of VER in wakefulness as well as in sleep. Diazepan increased considerably the amplitude of the last waves of the visual response. No significant changes were found with Meprobamate.

3. Changes of VER in the state of coma and stupor.

Aims of the work. In previous papers, changes of VER in natural sleep were described. It seemed of interest to establish whether in those clinical conditions where consciousness was greatly disturbed, there exist important changes in the visual inflow and whether some degree of regulation is still possible under these conditions.

Method of procedure. Forty experiments were performed in 22 stuporous patients and 6 experiments in 4 states of coma.

The same technique of continuous flicker stimulation was employed.

Results. In all these cases the response was simpler and of a lower amplitude than in normals.

In the state of coma the pattern of the response was very similar to the one

described in the newborn infant.

An overall reduction in amplitude as a function of time was observed in both circumstances. However, the changes were not so evident as in natural sleep.

In stuporous subjects important changes were observed in VER, generally in conjunction with modifications in the background activity, indicative of a change in the level of awareness. Nevertheless, for one same EEG level very important variations in the evoked potential were appreciable.

4. TRAVEL

García Austt was invited to participate in the Colloquium on "Mechanisms of Orienting Reaction in Man" sponsored by the Slovak Academy of Sciences, held in Bratislava. Czechoslovakia.

The following program was carried out :

1. September 11th, Saturday, 3-7 p.m., Castle of Smolenice :

The problem of stimulus specificity with regard to evoked potentials, EEG background activity changes and autonomic responses/heart rate, vasomotor activity, breathing, galvanic skin reflex/ in the course of the orienting reaction. Startle and the orienting reaction : similarities and dissimilarities.

A paper on "The problem of stimulus specificity with regard to evoked potentials" was presented at this meeting.

2. September 12th, Sunday, 9-12 a.m., Castle of Smolenice :

Sensory evoked potentials and eye movements, their place in the framework of the orienting reaction.

3. September 12th, Sunday, 3-6 p.m., Castle of Smolenice :

Related topics.

4. September 14th, Tuesday, 9-12 a.m., Bratislava, Hotel Devin :

Heart rate and respiratory changes elicited by the orienting reaction, their autonomy and/or interdependence. Physiological significance of the circulatory reactions/vasomotor activity, blood pressure/ in the course of physiological changes during the orienting reaction.

A paper on the "Changes of brain pO_2 in unrestrained cats during wakefulness and sleep" was submitted at this session.

5. September 14th, Tuesday, 3-6 p.m., Bratislava, Hotel Devin :

Excitability cycles in the EEG and autonomic responses to novel stimuli, with special regard to cycles with periodicities of about 1-2 minutes. This session was presided by García Austt.

6. September 15th, Wednesday, 9-12 a.m. Bratislava, Hotel Devin :

Effect of habituation on the sensory evoked potentials, EEG background activity and the vegetative component of the orienting reaction.

A paper was presented at this session on the "Changes of the scalp visual evoked response and EEG background activity in man during continuous flicker stimulation".

7. September 15th, Wednesday, 3-6 p.m., Bratislava, Hotel Devin :

Effect of various stages of vigilance, attention and sleep on the EEG, oculomotor and vegetative responses.

The following investigators intervened :

Balridge, B.J., M.D. (USA), Barlow, J., M.D. (USA), Baron, J.B., Dr. (France), Barrat, P.E.H., M.D. (Australia), Brezny, J., M.D. (Czechoslovakia), Ciganek, L., M.D. (Czechoslovakia), Creutzfeld, M., M.D. (Germany), Cernacek, J., M.D. (Czechoslovakia), Dixon, N.F., Ph.D. (England), Faidherbe, J., M.D. (Belgium), Figar, S., M.D. (Czechoslovakia), Fichtel, K., Dr. (Germany), Garcia-Austt, E., Dr. (Uruguay), Geer, J.H., M.D. (USA), Holubar, J., M.D. (Czechoslovakia), Hrbek, A., M.D. (Czechoslovakia), Hyman, Ch., Ph.D. (Sweden), Jung, R., M.D. (Germany), Kelleroval, E., M.D. (Czechoslovakia), Kimmel, H.D., M.D. (USA), Koepchen, H.P., Dr. (Germany), Larsson, E.L., M.D. (Sweden), Lindsley, D.B., Ph.D. (USA), Lorens, St. A. Jr., B.A. (USA), Luborski, M., M.D. (USA), Magnus, O., M.D. (The Netherlands), Manak, V., M.D. (Czechoslovakia), Naquet, R., Dr. (France), Obrist, P.A., Ph.D. (USA), Orlov, V.V., M.D. (USSR), Otto, E., Dr. (Germany), Pampiglione, G., M.D. (England), Pateisky, K., Dr. (Austria), Penaz, J., M.D. (Czechoslovakia), Prechtel, H.F.R., M.D. (Holland), Rémond, A., M.D. (France), Roth, B., M.D. (Czechoslovakia), Ruttkay-Nedecky, I., M.D. (Czechoslovakia), Servit, Zd., M.D. (Czechoslovakia), Spence, D., Ph.D. (USA), Unger,

S.M., M.D. (USA), Van Leeuwen, St., M.D. (The Netherlands), White, E.H., M.D. (USA), Zikmund, V., M.D. (Czechoslovakia).

After this meeting he visited the following scientific centers :

Institute of Physiology, Czechoslovak Academy of Sciences, Prague, Czechoslovakia ; Clinica Neurochirurgica, Universita di Genova, Ospedale S. Martino, Genova, Italia ; Istituto di Fisiologia, Universita di Pisa, Pisa, Italia ; Centro de Computazione, Universita di Pisa, Pisa, Italia ; Istituto di Patologia Speciale Medica e Metodologia Clinica, Ospedale di S. Maria della Scala, Siena, Italia ; Department of Neurological Surgery, New York, U.S.A., Department of Neurology, Albert Einstein College of Medicine, Yeshiva University, New York, U.S.A., Department of Psychology, Yale University, New Haven, Conn., U.S.A., Department of Physiology, Yale University, New Haven, Conn., U.S.A., Brain Research, University of Michigan, Ann Arbor, Michigan, U.S.A.

This travel was carried out with the grant funds assigned for this purpose.

5. MEETING REPORTS

Several investigations carried out under this grant were reported by Garcia Austt, by invitation, at the following regional or international meetings.

1. Round Table on "Sleep and Wakefulness" held in Vina del Mar, Chile on November 23-28, 1964 as a part of the VI Congress of the Latin-

american Association of Physiological Sciences.

2. VI Latin American Congress of Electroencephalography and Clinical Neurophysiology held in Sao Paulo, August 11-15, 1965.

3. Colloquium on "Mechanisms of Orienting Reaction in Man" held in Bratislava, September 11-15, 1965. From the three papers presented at this meeting, two of them ^{4,5} are related with the grant.

Prieto, Villar and Bachini read a co-report and Bogacz another one at the Sao Paulo meeting. Both co-reports submitted results obtained in connection with this research plan.

6. PUBLICATIONS

The paper on "Mecanismos neurofisiológicos de la vigilia y sus implicaciones psicológicas" presented at the Chile meeting has been published ².

The summaries of the papers presented in Sao Paulo have also been published ^{1,3,4}.

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2. García Austt, E. : Mecanismos neurofisiológicos de la vigilia y sus implicaciones psicológicas. Acta Neurol. Latinoamer., 1965, 11: 11-40.
3. García Austt, E. : Los potenciales sensoriales provocados como expresión del influjo de información. VI Congreso Latinoamericano de EEG, 1965, Sao Paulo, 11-15 de agosto. p. 178-180.

4. García Austt, E. : The problem of stimulus specificity with regard to evoked potentials. Orienting Reaction in Man. A Colloquium to be published by the Czechoslovak Academy of Sciences, 1965.
5. García Austt, E. : Changes of the scalp visual evoked response and EEG background activity in man during continuous flicker stimulation. Orienting Reaction in Man. A Colloquium to be published by the Czechoslovak Academy of Sciences, 1965.
6. Prieto, S., Villar, J.J. y Bachini, O. : Influencias farmacológicas sobre la respuesta visual provocada en el hombre. VI Congreso Latinoamericano de EEG, 1965. Sao Paulo, 11-15 de agosto. p. 185-186.

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13 ABSTRACT Objectives - (1) To establish changes observed in sensory evoked potential in normal subjects by barbiturates, lysergic acid, other psychotropic drugs in different attentional levels and during habituation and conditioning. (2) Same changes evoked in psychotic patients, especially schizophrenics. (3) The effect of these drugs on attention, habituation, and conditioning in rat, guinea pig, and cat. In the first year a beginning was made on objectives 1 and 2 adding sensory information on comatose and stuporous patients. The CAT computer system was modified to automate recording procedures allowing accumulation for present time, readout, erase and reset without operator action. Study of drug action was begun with LSD-25 on visual sensory inflow. Results: (1) multiplication of waves, particularly first components, (2) increase in amplitude, particularly last components. Experiments with drugs on neurotic and psychotic patients not yet definitive. Changes of VER in coma pattern of response similar to that of newborn infant; in stuporous subject changes were observed indicative of change in level of awareness.		